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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,725	ROSENBLUM, MICHAEL G.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,10,13-19,21 and 23-32* is/are pending in the application.

4a) Of the above claim(s) *15 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,10,13,14,16,21 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed January 22, 2008 in response to the Office Action of September 11, 2007, is acknowledged and has been entered. Claims 7, 10, 13-19, 21, and 23-32 are pending. No claims have been amended. Claims 15 and 17-19 remain withdrawn as drawn to a non-elected species. Claims 7, 10, 13, 14, 16, 21, and 23-32 are currently being examined.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. **Claims 7, 10, 13, 14, 21, 24-29, and 32 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 in view of US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, as evidenced by Kirkwood et al (J of Clinical Oncology, 1987, 5:1247-1255, IDS) (see section 3 of the previous Office Action).

The claims are drawn to a method of treating cancer in a human patient comprising a) identifying a patient having a tumor, which tumor comprises cells for targeting and wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites; b) obtaining a

composition comprising a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated to the biological response modifier, wherein it has been determined that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site; c) administering an amount of the composition to the patient effective to treat the cancer (claim 26), wherein the patient is diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells (claim 27), wherein the protein is an antibody (claim 28), wherein the antibody is a monoclonal antibody (claim 29), wherein the cancer is melanoma (claims 32 and 7), the method of claim 7 wherein the patient has been diagnosed with cancer and cells of the cancer express an antigen recognized by monoclonal antibody ZME-018, and further wherein the protein is a monoclonal antibody that recognizes and binds the antigen (claim 10), the method of claim 24 wherein the protein with an antigen recognition site is conjugated to the biological response modifier (claim 24), wherein the biological response modifier is a cytokine and is TNF (claims 13 and 14), the method of claim 14 or 24, wherein the protein's antigen recognition site recognizes and binds the ZME-018 antigen, an antigen recognized by monoclonal antibody ZME-018 (claim 25 or 21, respectively).

Scannon et al teach a method of treating melanoma in humans comprising administering an antibody-ricin A toxin conjugate, wherein the antibody of the conjugate binds the melanoma-specific antigen of 240kD and is a monoclonal antibody (abstract; col. 5, lines 27-60; col. 7, lines 30-50; Table II). Scannon et al teach that the 240kD

antigen is specifically expressed in melanoma, hence the antigen would be a cell surface antigenic marker at a concentration in excess of that found at non-target sites (col. 6, lines 21-27). The human patient treated with the antibody conjugate specific for melanoma would necessarily have been identified or diagnosed as a patient having a melanoma tumor and the patient's melanoma would be expressing the melanoma-specific antigen targeted by the antibody conjugate for killing tumor cells. An antibody conjugate composition is obtained because it had to be obtained in order to be administered. Scannon et al teach that the antibody-toxin conjugate allows for specific targeting of toxins to melanoma for human melanoma therapy because of selective binding activity of the antibody for the melanoma-specific antigen (col. 1, lines 55-68).

As evidence by Kirkwood et al, the XME-018 antibody binds to gp240, a 240kD melanoma-associated antigen that has exhibited greater restriction to melanoma than other antigens (p. 1247). US Patent 4,590,071 does not teach that the 240kD antigen is gp240, however, the claimed antigen appears to be the same as the prior art antigen that ZME-018 antibody recognizes, hence Scannon et al teach that an antibody of the antibody-conjugate that binds the same antigen recognized by antibody ZME-018. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Scannon et al does not teach that the antibody is conjugated to a biological response modifier and that the modifier is TNF.

Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to toxic drugs such as ricin A toxin and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of preparing immunoconjugates are known in the art (col. 3, lines 17-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the ricin A toxin of the antibody conjugate taught by Scannon et al because Ferris teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody. One would have been motivated to use an antibody-TNF conjugate in the method of Scannon et al in order to selectively kill melanoma cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat melanoma in a human patient because the antibody taught by Scannon et al successfully and specifically targets a toxin to human melanoma cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody- ricin A toxin conjugate taught by Scannon et al had a known function for treating melanoma by targeting the toxin to melanoma that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the ricin toxin), and the results of the substitution would have been predictable for treatment.

Response to Arguments

3. Applicants argue that they cannot find anywhere that the Scannon reference teaches or suggests that the 240kD antigen is a cell surface antigen and that the Action fails to identify any such teaching. Applicants argue that there is no way of knowing from Scannon whether the 240kD antigen is a cell surface antigen or not. Applicants point to US Patent 4,894,227 ("Stevens") and argue that Stevens teaches a 240kD intracellular protein antigen that can serve as a target for immunotoxin therapy for melanoma. Applicants argue that some 240kD tumor antigens are intracellular in nature. Applicants argue that the "gp240" antigen taught by Kirkwood is not necessarily the 240kD antigen of Scannon and that Scannon does not teach that the 240kD antigen is a glycoprotein (p. 5-6).

The arguments have been considered but are not found persuasive. Solely in response to Applicants' arguments, Examiner has provided references that demonstrate evidence that the antibody conjugates taught by Scannon inherently bind the cell

surface melanoma antigen recognized by antibody ZME-018, hence the issues remain the same. It is noted that Scannon refers to the antibody-RTA conjugates as "XMMME-001-RTA" or "XMMME-RTA-002" (see col. 5, lines 45-60; col. 6, lines 4-27; Table 1; col. 7, lines 31-51; Table II; all claims).

1) Ashcroft et al (Chem Commun, 2006, p. 3004-3006) provide evidence that ZME-018 antigen (to which ZME-018 antibody binds and recognizes) is also known as "gp240" and "high molecular weight melanoma-associated antigen (HMWMAA)" (p. 3004, col. 1).

2) Ferrone et al (J of Dermatology, December 1988, 457-465) provide evidence that HMWMAA (HMW-MAA) is a cell surface antigen (Table 1).

3) Martin et al (Human Gene Therapy, 1998, 9:737-746) provide evidence that XMMME-001-RTA binds HWAMAA. Martin et al teach that antibodies directed against HMWMAA have been used clinically to target toxic agents to melanomas and points to Oratz et al (below) as an immunoconjugate directed against HMWMAA.

4) Oratz et al (J Biol Response Mod, 1990, 9:345-354) as referred to by Martin et al (above), teach using XMMME-001-RTA immunoconjugate to treat patients with melanoma, hence XMMME-001-RTA, as referred to by Martin et al, is an immunoconjugate that binds HMWMAA (abstract, see entire paper). Further, Oratz et al teach that XMMME-001-RTA is the immunoconjugate described in US Patent 4,590,071, Scannon et al (p. 346, col. 2, reference #9).

Given the evidence above, it is clear that the antibody conjugate taught by Scannon inherently binds the cell surface antigen recognized by monoclonal antibody ZME-018, hence the issues remain the same.

4. Applicants argue that the Action reads into the reference an assumption that Scannon teaches 1) that "cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site" (claim 26), and 2) that the patient is "diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells" (claim 27). Applicants argue that Examiner does not point to a teaching and does not cite language from Scannon in support of this conclusion. Applicants argue that they cannot find such teaching in Scannon that teaches or suggests the invention of claims 26 and 27 (p. 6-7).

The arguments have been considered but are not found persuasive. With regards to point 1) of Applicants, Applicants are arguing an inherent property of the patient's tumor. Examiner points to the rejection of section 3 in the previous Office Action (section 2 above): "Scannon et al teach a method of treating melanoma in humans comprising administering an antibody-ricin A toxin conjugate, wherein the antibody of the conjugate binds the melanoma-specific antigen of 240kD and is a monoclonal antibody (abstract; col. 5, lines 27-60; col. 7, lines 30-50; Table II)." Clearly, Examiner pointed to teachings by Scannon for the treatment of human patients with melanoma, particularly the abstract and col. 5, lines 27-60. Examiner further points to

teachings that melanoma expresses the 240kD antigen specifically (also known as ZME-018 antigen or HMW-MAA antigen) which is recognized and bound by the immunoconjugates taught by Scannon: "Scannon et al teach that the 240kD antigen is specifically expressed in melanoma, hence the antigen would be a cell surface antigenic marker at a concentration in excess of that found at non-target sites (col. 6, lines 21-27)." Clearly, Scannon teaches the human patient treated was identified as having melanoma, and Scannon teaches that melanoma specifically expresses the 240kD antigen recognized and bound by the immunoconjugates taught by Scannon. It was determined in Scannon that the melanoma in the human patient expresses a 240kD antigen recognized and bound by the immunoconjugates taught by Scannon, hence melanoma inherently "expresses an antigen recognized and bound by the protein with an antigen recognition site."

With regards to point 2) of Applicants, which requires a biological response modifier, Applicants are arguing the individual Scannon reference. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, Applicants are arguing an inherent property of the patient's tumor. As stated in the previous Office Action section 3: "Scannon et al teach that the 240kD antigen is specifically expressed in melanoma, hence the antigen would be a cell surface antigenic marker at a concentration in excess of that found at non-target sites (col. 6, lines 21-27). The human patient treated with the antibody conjugate specific for melanoma would necessarily have been identified or diagnosed as a patient having a melanoma tumor and the patient's melanoma would be expressing the melanoma-specific antigen targeted by the antibody conjugate for killing tumor cells...Scannon et al teach that the antibody-toxin conjugate allows for specific targeting of toxins to melanoma for human melanoma therapy because of selective binding activity of the antibody for the melanoma-specific antigen (col. 1, lines 55-68)." Clearly, the patients diagnosed with melanoma have a tumor that is known to specifically express the cell surface 240kD antigen, hence the antigen would be a cell surface antigenic marker at a concentration in excess of that found at non-target sites. Given that Scannon et al teach that the antibody-toxin conjugate allows for specific targeting of toxins to melanoma for human melanoma therapy because of selective binding activity of the antibody for the melanoma-specific antigen, clearly, the melanoma tumor expressing the cell surface 240kD antigen would allow targeting and concentration of the antibody-toxin conjugate at the site of the tumor where it is needed to kill tumor cells. In combination with Ferris et al, Scannon and Ferris et al teach it is obvious to conjugate TNF (biological response modifier) to an antibody for the treatment of cancer, hence the melanoma tumor expressing the cell surface 240kD antigen would allow targeting and concentration of

the antibody-TNF conjugate, given the antibody is responsible for the targeting. Claims 7, 10, 13, 14, 21, 24-29, and 32 remain rejected under 35 U.S.C. 103(a) for the reasons of record.

5. **Claim 16 remains rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 and US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, as applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of Blick et al (Cancer Research, 1987, 47:2986-2989) (see section 4 of the previous Office Action).

The claim is drawn to the method of claim 14 wherein the TNF is TNF-alpha.

Scannon et al and Ferris et al teach a method of treating melanoma in a human comprising identifying a patient having melanoma, of which the melanoma express a cell surface antigen found in excess of that found at other non-target sites, obtaining and administering an antibody-TNF conjugate wherein the antibody binds the melanoma antigen and allows for specific delivery of the TNF to melanoma cells as set forth above.

Scannon et al and Ferris et al do not teach that the TNF is TNF-alpha.

Blick et al teach a method of treating cancer in a human patient with TNF-alpha with evidence of antitumor effects for some patients (p. 2988, col. 1; p. 2989, col. 1). It is well known in the art and the reference teaches that cytokines are known to have cytostatic and cytotoxic effects against a wide range of human tumor cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use TNF-alpha taught by Blick et al as the TNF conjugated to the antibody taught by Scannon et al and Ferris et al because TNF-alpha is a well known biological response modifier that has antitumor activity and is a natural defense against tumors produced by activated macrophages. One would have been motivated to use the TNF-alpha as the TNF of the antibody conjugate in order to specifically kill tumor cells. One would have a reasonable expectation of success treating melanoma using an antibody-TNF-alpha conjugate because of its known antitumor effects.

Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF-alpha for the TNF), and the results of the substitution would have been predictable.

Response to Arguments

6. Applicants incorporate the arguments as set forth above. Applicants argue that Blick merely relates to a phase I study using unconjugated TNF alpha and argues that this does not teach or suggest targeted TNF alpha conjugate. Applicants argue that there is no evidence of record that such a conjugate would retain TNF activity. Applicants argue that Blick does not teach immunotoxin or targeted therapy. Applicants argue that Blick is not relevant and the Action fails to explain why one of skill would use TNF alpha in a targeted construct and expect that such a construct would maintain TNF alpha activity (p. 7).

The previous arguments drawn to Scannon have been considered and were not found persuasive for the reasons set forth above. The current arguments have been considered but are not found persuasive because Applicants have argued and discussed the Blick reference individually without clearly addressing the combined teachings. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants are directed to the rejection of section 3 in the previous Office Action (section 2 above) that states: "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the ricin A toxin of the antibody conjugate taught by Scannon et al because Ferris teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody." Applicants are pointed to the teaching of Ferris et al: "Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to toxic drugs such as ricin A toxin and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of

preparing immunoconjugates are known in the art (col. 3, lines 17-21)." Given that Blick et al teach TNF-alpha, a type of TNF, has known antitumor effects and it is well known in the art and the reference teaches that cytokines are known to have cytostatic and cytotoxic effects against a wide range of human tumor cells, one of skill in the art could have substituted one known element for another (the TNF-alpha for the generic TNF), and the results of the substitution would have been predictable. Given the known methods of making TNF-antibody conjugates, and the known antitumor function of TNF or TNF-alpha, clearly, and contrary to Applicants' assertions, one of skill in the art would have a reasonable expectation of success treating melanoma using an antibody-TNF-alpha conjugate because of its known antitumor effects. Applicants do not support their assertions as to why one of skill in the art would *not* have a reasonable expectation of success using the TNF-alpha antibody conjugate and why the TNF-alpha antibody conjugate would *not* retain TNF-alpha function, despite the teachings of the combined references. MPEP 716.01(c)states: "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." The claims remain obvious in view of the combined references.

7. **Claim 23 remains rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 and US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, as applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of Ghose et al (Crit Rev Ther Drug Carrier Syst, 1987, 3:263-359) (see section 5 of the previous office Action).

The claim is drawn to the method of claim 26, wherein the protein with an antigen recognition site is fused to the biological response modifier.

Scannon et al and Ferris et al teach a method of treating melanoma in a human comprising identifying a patient having melanoma, of which the melanoma express a cell surface antigen found in excess of that found at other non-target sites, obtaining and administering an antibody-TNF conjugate wherein the antibody binds the melanoma antigen and allows for specific delivery of the TNF to melanoma cells as set forth above. Ferris et al further teach the recombinant production of TNF (Example 3, col. 6).

Scannon et al and Ferris et al do not teach that the antibody is fused to the biological response modifier (or TNF).

Ghose et al teach recombinant technology to create hybrid antibody molecules that are directed against the tumor-associated antigen and linked to biological products with antitumor activity such as tumor necrosis factor (p. 334). Ghose et al also teach the advantage of a fused molecule over a conjugated molecule because fused molecules produced from transfection methods are more likely to be free of contaminating oncogenic viruses and nucleic acids as opposed to monoclonal antibodies produced by

malignant cells used for conjugation to a biological response modifier (p. 334). Ghose et al teach the advantage of a fused molecule as a "tailored antibody molecule" (p. 334) wherein genetic engineering can create one molecule to both target and treat a cancer cell.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an antibody fused to a biological response modifier as taught by Ghose et al into the method of Scannon et al and Ferris et al in order to make a fused "tailored" immunoconjugate free of contaminants for treating cancer. One would have been motivated to incorporate an antibody fused to a biological response modifier into the method taught by Scannon et al and Ferris et al because Ghose et al teach the advantages of being able to tailor a fused molecule to comprise the desired target antibody and biological response modifier, and the production of fused molecules resulting in less contamination, a factor important in the manufacture of drugs for treating cancer in human patients. One would have a reasonable expectation of success using a fused antibody-biological response modifier molecule in the method taught by Scannon et al and Ferris et al because the fused antibody molecule serves the same function as the conjugated antibody molecule.

Given the known technology for making recombinant or fused antibodies, and given the known functions of the antibody and biological response modifier, one of skill in the art could have substituted one known element for another (the fused antibody for the conjugated antibody), and the results of the substitution would have been predictable for cancer treatment.

Response to Arguments

8. Applicants incorporate the arguments as set forth above. Applicants argue that Ghose is not relevant to the primary basis of the rejection (p. 7).

The previous arguments drawn to Scannon have been considered and were not found persuasive for the reasons set forth above. Ghose, in combination with Scannon and Ferris render obvious the claimed method for the reasons set forth previously in section 5 (section 7 above).

9. **Claims 7, 24, 26-29, and 30 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,753,894, Frankel et al, filed 1/11/1985, issued 6/28/1988 in view of US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988 (see section 6 of the previous office Action).

The claims are drawn to a method of treating cancer in a human patient comprising a) identifying a patient having a tumor, which tumor comprises cells for targeting and wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites; b) obtaining a composition comprising a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated to the biological response modifier, wherein it has been determined that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site; c) administering an amount of the composition to the patient effective to treat the cancer (claim 26), wherein the protein with an antigen recognition site is conjugated to the biological response modifier

(claim 24), wherein the patient is diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells (claim 27), wherein the protein is an antibody (claim 28), wherein the antibody is a monoclonal antibody (claim 29), wherein said cancer is breast cancer (claim 7 and 30).

Frankel et al teach a method of treating breast cancer in a human comprising administering an antibody-ricin A toxin conjugate wherein the antibody binds a breast cancer antigen that is a cell surface antigen expressed at higher concentrations on the breast cancer compared to that found on normal tissue, non-target sites, and wherein the antibody is monoclonal (abstract; col. 3, line 16 through col. 5, line 52; Tables 1 and 2; col. 14, line 50 through col. 15, line 10; Table 6). The patient treated with the antibody conjugate specific for breast cancer would necessarily have been identified or diagnosed as a patient having a breast tumor and the patient's breast cancer would be expressing the breast cancer-specific antigen targeted by the antibody conjugate for killing tumor cells. An antibody conjugate composition is obtained because it had to be obtained in order to be administered.

Frankel et al does not teach that the antibody is conjugated to a biological response modifier.

Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to toxic drugs such as ricin A and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue

of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of preparing immunoconjugates are known in the art (col. 3, lines 17-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the ricin A toxin of the antibody conjugate taught by Frankel et al because Ferris teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody. One would have been motivated to use an antibody-TNF conjugate in the method of Frankel et al in order to selectively kill breast cancer cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat breast cancer in a human patient because the antibody taught by Frankel et al successfully and specifically targets a toxin to human breast cancer cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody- ricin toxin conjugate taught by Frankel et al had a known function for treating breast cancer by targeting the toxin to breast cancer cells that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the ricin A toxin), and the results of the substitution would have been predictable for cancer treatment.

Response to Arguments

10. Applicants argue that the Action reads into the reference an assumption that Frankel teaches 1) that "cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site" (claim 26) and 2) that the patient is "diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells" (claim 27). Applicants argue that they cannot find such teaching in Frankel that teaches or suggests the invention of claims 26 and 27 (p. 8-9).

The arguments have been considered but are not found persuasive because Frankel does teach every active step of the claims and Applicants are arguing the inherent nature of the patient's cancer. With regards to Applicants' point 1), Frankel clearly teaches that breast cancer is determined to express an antigen that the antibodies, of the antibody-ricin-A toxin immunoconjugates, recognize and bind (Table 2). Given the breast cancer patients being treated with the immunoconjugates are identified as having breast cancer, the cells of the breast tumor in the patient would express an antigen recognized and bound by the antibodies in the immunoconjugates taught by Frankel. Therefore, the "cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site."

With regards to Applicants' point 2), as stated above, Frankel clearly teaches that breast cancer is determined to express an antigen that the antibodies of the immunoconjugates recognize and bind (Table 2), further, these antibodies were determined not to bind to other normal tissues (Table 1), hence the antigens are

necessarily a specific antigenic determinant of breast cancer. Given the antigens are expressed on breast cancer and not on other normal tissues, and given the antibodies are demonstrated to bind specifically to breast cancer, the immunoconjugates comprising these antibodies would target and concentrate a biological response modifier at the breast cancer or breast tumor. Therefore, the breast cancer patients taught by Frankel would necessarily have a breast tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells. The claims remain obvious in view of the combined references.

11. **Claims 7, 24, 26-29, 31 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,666,845, Mattes et al, filed 12/16/1983, 4,666,845 in view of US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988 (see section 7 of the previous Office Action).

The claims are drawn to a method of treating cancer in a human patient comprising a) identifying a patient having a tumor, which tumor comprises cells for targeting and wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites; b) obtaining a composition comprising a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated to the biological response modifier, wherein it has been determined that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site; c) administering an amount of

the composition to the patient effective to treat the cancer (claim 26), wherein the protein with an antigen recognition site is conjugated to the biological response modifier (claim 24), wherein the patient is diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells (claim 27), wherein the protein is an antibody (claim 28), wherein the antibody is a monoclonal antibody (claim 29), wherein said cancer is cervical carcinoma (claim 7 and 31).

Mattes et al teach a method for treating cervical carcinoma in a human comprising administering a monoclonal antibody, MH49, conjugated to a toxin to kill cancer cells (col. 14, lines 27-40). Mattes et al teach that monoclonal antibody MH49 binds to an antigen found on human cervical carcinoma cells at concentrations in excess of that found in other tissues (Table I, Table II, col. 4, lines 15-15; col. 11, line 55 through col. 12, line 18; col. 13, lines 1-11). Mattes et al teach methods of diagnosis using the monoclonal antibody tagged with a radioactive label for localizing cervical carcinoma in a patient (col. 14, lines 19-26). The patient treated with the antibody conjugate specific for cervical carcinoma would necessarily have been identified or diagnosed as a patient having a cervical carcinoma and the patient's cervical carcinoma would be expressing the cervical carcinoma -specific antigen targeted by the antibody conjugate administered for killing tumor cells. An antibody conjugate composition is obtained because it had to be obtained in order to be administered.

Mattes et al does not teach that the antibody is conjugated to a biological response modifier.

Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to toxic drugs such as ricin A toxin and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of preparing immunoconjugates are known in the art (col. 3, lines 17-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the toxin of the antibody conjugate taught by Mattes et al because Ferris teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody. One would have been motivated to use an antibody-TNF conjugate in the method of Mattes et al in order to selectively kill cervical carcinoma cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat cervical carcinoma in a human patient because the antibody taught by Mattes et al targets a toxin to human cervical carcinoma cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody-toxin conjugate taught by Mattes et al has a known function for treating cervical carcinoma by targeting the toxin to cervical carcinoma cells that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the

toxin), and the results of the substitution would have been predictable for cancer treatment.

Response to Arguments

12. Applicants argue that the Action does not point out or comment upon Mattes with respect to the identifying and diagnosing elements of claims 26 and 27. Applicants argue that Ferris is cited for other matters and is deemed irrelevant to the issue (p. 9).

The arguments have been considered but are not found persuasive because Mattes does teach the identifying and diagnosing elements of claims 26 and 27 and the inherent nature of the patient's cervical carcinoma. Mattes teaches that cervical carcinoma expresses a cell surface antigen recognized by antibody MH49 (abstract; col. 13, lines 1-11; Table I and II). Mattes teaches methods of diagnosis (i.e. identifying a patient with cervical carcinoma that expresses the antigen bound by MH49) using the monoclonal antibody (MH94) tagged with a radioactive label for localizing cervical carcinoma in a patient (col. 14, lines 19-26). Mattes teaches a method for treating cervical carcinoma in a human comprising administering a monoclonal antibody, MH49, conjugated to a toxin to kill cancer cells (col. 14, lines 27-40). Given the cervical carcinoma patients being treated with the immunoconjugates are identified as having cervical carcinoma, the cells of the cervical carcinoma in the patient would express an antigen recognized and bound by the antibody MH49 in the immunoconjugates taught by Frankel. Therefore, the "cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site."

Further, Mattes clearly teaches that cervical carcinoma is determined to express an antigen that the antibody, MH49, of the immunoconjugate recognizes and binds (abstract; col. 13, lines 1-11; Table I and II), and this antibody was determined not to bind extensively to other tissues (col. 13, lines 1-11; Table I and II), hence the antigen is necessarily a specific antigenic determinant of cervical carcinoma. Given the antigen is expressed on cervical carcinoma and not extensively on other tissues, and given the antibody is demonstrated to bind specifically to cervical carcinoma, the immunoconjugates comprising antibody MH49 would target and concentrate a biological response modifier at the breast cancer or breast tumor. Therefore, the breast cancer patients taught by Mattes would necessarily have a cervical carcinoma tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells. The claims remain obvious in view of the combined references.

13. **Conclusion:** No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL

EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643